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Losartan treatment for non-alcoholic steatohepatitis (NASH)

Submission date 07/10/2009	**Recruitment status** No longer recruiting	[X] Prospectively registered [_] Protocol
Registration date 12/10/2009	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 19/04/2017	**Condition category** Digestive System	[_] Individual participant data

Plain English summary of protocol

Background and study aims
As many as 1 in 10 people have some form of liver disorder which can cause problems ranging from impaired quality of life to more serious complications including liver failure. Fibrosis is the accumulation of tough scar tissue in the liver, and occurs in patients with non-alcoholic steatohepatitis (NASH). The major feature of NASH is fat in the liver, along with inflammation and damage of the liver tissue. This can lead to permanent damage of the liver, which prevents it from functioning properly. Currently there are no available treatments aimed at slowing down or stopping the progression of fibrosis of the liver. Previous studies have demonstrated that drugs similar to Losartan help to reduce the inflammation. These studies would lead us to believe that Losartan will be effective in patients with NASH. This study aims to test Losartan in patients with fibrosis associated with NASH.

Who can participate?
Adults (both males and females, aged 18+) with fibrosis resulting from NASH.

What does the study involve?
Sometimes we need to find out how effective a study drug is by comparing two groups of patients with the same illness. We do this by giving the study tablet/capsule (Losartan) to one group and an identical looking tablet/capsule (the placebo), which contains inactive ingredients, to the other group. To try to make sure the groups are the same to start with, each patient is put into a group by chance (randomly – like tossing a coin). Neither you, your doctor, nor your spouse /family will know whether you are receiving Losartan or the placebo, as both will look exactly the same. We call this type of study a double-blind study. If your doctor needs to find out which treatment group you are in, then he or she may do so. You will take a study tablet/capsule once a day for up to two years. The study results will then be compared to see how effective the study drug is compared with the placebo. For the purposes of this study, you will attend your hospital outpatient department or research centre on nine occasions. On each of the nine occasions that you attend the hospital, your study assessment will take about 30 minutes, apart from your first visit which may take up to two hours. The assessments will be conducted by the research team, which includes a research doctor specializing in liver disease, as well as other trained research personnel. If you agree to be part of the study, you will be invited to sign the consent form before undergoing any research-related assessments. The sponsor of the study

(Newcastle upon Tyne Hospitals NHS Foundation Trust) is currently in collaboration with GlaxoSmithKline who have requested the collection of extra blood samples to be collected at all of the visits, except visit three (week one). This will be explained to you by the Research Doctor, and you will be invited to participate in this separate voluntary study.

What are the possible benefits and risks of participating?
There may be no direct benefit to you from taking part. However, this study will help us to find out if Losartan is useful in slowing down, stopping or reversing liver fibrosis. We are unable to promise that the study will help you, but it may help patients in the future. There are no major disadvantages or risks in taking part in this study. Because we ask for some blood samples there is a small risk of bruising or discomfort at the injection site. A liver biopsy will be carried out at visit 8 (96 weeks). Up to one in three patients may experience some pain or discomfort following the biopsy. This may last two or three days. Usually a mild painkiller such as paracetamol is all that is need to treat this pain. Serious bleeding occurs in approximately one in 300 patients. This may require a blood transfusion or another procedure to stop it. Less than one in 1000 patients may have another organ punctured, such as lung, kidney or colon. This might cause pain or breathlessness, but would resolve itself without any further treatment. In less than one in 1000 patients, leakage of bile from the biopsy site into the abdomen may occur. This might cause pain in the abdomen but also usually resolves with no specific treatment. Patients with some conditions have an increased risk of infection after a liver biopsy. If we suspect that you have one of these conditions we will give you intravenous antibiotics before the biopsy. Slight discomfort may occur up to seven days after the biopsy, and you must inform your GP if this becomes severe or you develop swelling. Every effort will be made to keep you comfortable during this procedure. You will need to stay in hospital for six hours following the biopsy and possibly overnight after this procedure, but your doctor will discuss this with you prior to the procedure.

Where is the study run from?
Newcastle University (UK)

When is the study starting and how long is it expected to run for?
May 2011 to October 2014

Who is funding the study?
Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

ClinicalTrials.gov (NCT)
NCT01051219

Protocol serial number

Study information

Scientific Title
A randomised controlled trial of losartan as an anti-fibrotic agent in non-alcoholic steatohepatitis

Acronym
FELINE (anti-Fibrotic Effects of Losartan In Nash Evaluation study)

Study objectives
Primary hypothesis:
That losartan is superior to placebo in reversing, slowing down or halting fibrosis in patients with non-alcoholic fatty liver disease, after 24 months of treatment.

Secondary hypothesis:
1. That the safety profile of the angiotensin receptor blocker (losartan) in this patient population is acceptable
2. That losartan can prevent clinical deterioration in non-alcoholic fatty liver disease
3. That serum, radiological and histological markers of fibrosis correlate in these patients over a 24 month period

Ethics approval required
Old ethics approval format

Ethics approval(s)
Sunderland Research Ethics Committee, 23/03/2010, ref: 10/H0904/8

Study design
Randomised parallel-group double-blind placebo-controlled study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Fibrosis resulting from non-alcoholic steatohepatitis

Interventions
Treatment group: losartan orally, 50 mg capsule once a day for 24 months.
Control group: matched placebo orally, 1 capsule daily for 24 months.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Losartan

Primary outcome(s)
Kleiner fibrosis score, based on histological fibrosis stage at trial entry and end of study (96 weeks)

Key secondary outcome(s))
1. Measurement of change in fibroscan score performed at trial entry, 48 weeks and end of study
2. Serological (Enhanced Liver Fibrosis test [ELF™ test]) markers of fibrosis performed at trial entry, 48 weeks and end of study
3. Change in non-alcoholic fatty liver disease (NAFLD) activity score (NAS) from baseline, determined by liver biopsy at trial entry and end of study

Completion date
01/10/2014

Eligibility

Key inclusion criteria
Current inclusion criteria as of 16/06/2011:
Adults (both males and females, aged 18+) with steatohepatitis and fibrosis (Kleiner F1-F3), resulting from non-alcoholic fatty liver disease

Previous inclusion criteria:
Adults (both males and females, aged 18+) with fibrosis resulting from non-alcoholic steatohepatitis.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Current exclusion criteria as of 09/07/2012:
1. Refusal or inability (lack of capacity) to give informed consent
2. Average alcohol ingestion >21 units/week (males) or >14 units/week (females)
3. History or presence of Type 1 diabetes mellitus
4. Haemoglobin A1C >15.0
5. Other causes of chronic liver disease or hepatic steatosis

6. Any contra-indication to liver biopsy
7. History of or planned gastrointestinal bypass surgery
8. Hepatocellular carcinoma
9. Previous liver transplantation
10. Recent significant weight loss (>5% total body weight within last 6 months)
11. Electrolyte disturbance: potassium level outside the normal (local) range.
12. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >10 x upper limit of normal (ULN) at screening
13. Recent (within 6 months of baseline liver biopsy and screening visit) or concomitant use of agent known to cause hepatic steatosis (corticosteroids, amiodarone, methotrexate, tamoxifen, tetracycline, high dose oestrogens, valproic acid) or concomitant use of pioglitazone, fluconazole, rifampicin or any drug contra-indicated in the Losartan SmPC.
14. Introduction of metformin, glitazones, a GLP-1 agonist, Vitamin E or C, betaine, s-adenosyl methionine, ursodeoxycholic acid, silymarin, fibrate, pentoxifylline, orlistat, sibutramine or rimonabant within 3 months of baseline liver biopsy and screening visit.
15. Intolerance of angiotensin receptor blockers (ARBs) or presence of multiple allergic reactions to drugs
16. Use of angiotensin-converting enzyme (ACE) inhibitor or ARB in previous year
17. Hypotension (systolic <100, diastolic <60)
18. Renal failure (Cr >130)
19. Participation in any clinical study of an investigational agent within 30 days or five half-lives of the investigational product, whichever is longer
20. Presence of clinically relevant cardiovascular, pulmonary, gastro-intestinal, renal, hepatic, metabolic, haematological, neurological, psychiatric, systemic, ocular, gynaecologic or any acute infectious disease or signs of acute illness that, in the opinion of the investigator, might compromise the patient's safe participation in the trial
21. Presence or history of cancer within the past 5 years with exception of adequately treated localised basal cell carcinoma of the skin, in situ cervical carcinoma or solid malignancy surgically excised in toto without recurrence for five years
22. Women of child-bearing potential not protected by effective contraceptive method of birth control or surgical sterilization and/or who are unwilling or unable to be tested for pregnancy (Pregnancy status will be checked by serum pregnancy testing before initiation of study treatment and by urine pregnancy testing during the trial)
23. Known allergy or sensitivity to losartan or its excipients (microcrystalline cellulose [E460]; lactose monohydrate; pregelaatinized maize starch; magnesium stearate [E572]; hydroxypropyl cellulose [E463]; hypromellose [E464])

Previous exclusion criteria until 09/07/2012:
4. Haemoglobin A1C>9.0
14. Recent (within 3 months of baseline liver biopsy and screening visit) change in anti-diabetes treatment or change in dose or regimen, or introduction of Vitamin E or C, betaine, s-adenosyl methionine, ursodeoxycholic acid, silymarin, fibrate, pentoxifylline, orlistat, sibutramine or rimonabant.

Previous exclusion criteria:
4. Haemoglobin A1C >8.5
12. Recent (within 6 months of baseline liver biopsy and screening visit) or concomitant use of agent known to cause hepatic steatosis (corticosteroids, amiodarone, methotrexate, tamoxifen, tetracycline, high dose oestrogens, valproic acid)
13. Recent (within 3 months of baseline liver biopsy and screening visit) change in anti-diabetes treatment
14. Recent (within 6 months of baseline liver biopsy and screening visit) or concomitant use of

pioglitazone, fluconazole, rifampicin or any drug contra-indicated in the losartan SmPC
15. Recent (within 3 months of baseline liver biopsy and screening visit) change in dose/regimen or introduction of vitamin E or C, betaine, s-adenosyl methionine, ursodeoxycholic acid, silymarin, fibrate or pentoxifylline
20. Decompensated cirrhosis Childs-Pugh Class B or C (score >6)

Date of first enrolment
30/06/2011

Date of final enrolment
18/10/2012

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Birmingham University Hospital NHS Foundation Trust
Queen Elizabeth Hospital
Edgbaston
Birmingham
United Kingdom
B15 2TH

Study participating centre
Cambridge University NHS Trust
Addenbrooke's Hospital
Hills Road
Cambridge
United Kingdom
CB2 0QQ

Study participating centre
Guy's & St Thomas's NHS Foundation Trust
Westminster Bridge Road
London
United Kingdom
SE1 7EH

Study participating centre

Imperial College NHS Trust
St Mary’s Hospital
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United Kingdom
W2 1NY

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Clinical Research Facility
Level 6, Leazes Wing
Newcastle upon Tyne
United Kingdom
NE1 4LP

Study participating centre
Nottingham University Hospitals NHS Trust
Queens Medical Centre Campus
Derby Road
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NG7 2UH

Study participating centre
Plymouth Hospitals NHS Foundation Trust
Derriford Hospital
Derriford Road
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Study participating centre
St George's Healthcare NHS Trust
Dept. of Gastroenterology and Hepatology
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Derby Hospitals NHS Foundation Trust
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Royal Liverpool & Broadgreen University Hospitals NHS Trust
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4th Floor Linda McCartney Centre
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Government

Funder Name
Medical Research Council (MRC)/National Institutes of Health Research (NIHR) (UK) - Efficacy and Mechanism Evaluation (EME) Programme (ref: EME 08/43/15)

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	18/04/2017		Yes	No
HRA research summary			28/06/2023	No	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes